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Original article

Is radiographic progression of late-onset rheumatoid arthritis different from young-onset rheumatoid arthritis? Results from the Swiss prospective observational cohort

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Abstract

Objective. RA can be categorized into late-onset RA (LORA, >60–65 years) and young-onset RA (YORA, 30–55 years), depending on the patient's age at disease onset. Since the average age of the population is continuously increasing, LORA will most probably gain in importance in the future. Despite this growing importance, LORA has not been the focus of much interest in the past. The aim of this study was to analyse radiographic damage progression of early disease in LORA compared with YORA patients.

Methods. We included all patients from the Swiss RA registry, Swiss Clinical Quality Management in RA, with recent-onset arthritis, either RA (disease duration $\leqslant$1 year) or undifferentiated arthritis, as diagnosed by the data-entering physician. Patients were followed for 5 years. The cut-off between YORA and LORA was operationally set at 60 years of age. The primary outcome of this study was disease progression and activity, which was assessed based on the 28-joint DAS (DAS28) and the progression of joint erosions using a validated scoring system (Ratingen score).

Results. A total of 592 patients with early disease were analysed. The age at disease onset had a Gaussian distribution, with a single peak at 54 years of age; 366 patients were categorized as YORA and 226 as LORA at disease onset. DAS28 scores were significantly higher among LORA as compared with YORA patients (4.8 *vs* 4.5, $P = 0.049$). Corticosteroids were used in 68% of LORA patients as a first-line treatment, compared with 25.4% in YORA patients (χ^2 test: 54.58; $P < 0.0001$). In contrast, DMARDs were used in 100% of the YORA patients as first-line treatment, compared with 91.2% of the LORA patients. During follow-up, new glucocorticoids, synthetic DMARDs or biologic DMARDs were initiated in 32.8%, 61.1% and 14.1% of all YORA patients and 17.5%, 54.6% and 6.6% of LORA patients, respectively (χ^2 test: 7.08, 22.53, 54.4; all $P < 0.01$). The DAS28 scores decreased in both groups during the observed time period, and the initial differences in disease activity vanished after 6 months and during the subsequent follow-up. The Ratingen score was higher in LORA than in YORA patients at inclusion (12.7 *vs* 5.6, $P < 0.0001$). The rate of radiographic progression at 5 years was similar when comparing LORA and YORA (3.3 *vs* 2.6, respectively, $P = 0.64$). The Ratingen scores at onset and during follow-up over 5 years did not clearly separate LORA and YORA into two groups, but rather, increased linearly when comparing the patients in groups per decade from 20 to 92 years of age.

Conclusion. Our results did not show LORA as a separate subgroup of RA with a different prognosis with regard to radiographic progression.

Key words: rheumatoid arthritis, radiographic progression, elderly, DAS28, HAQ, early disease.

CLINICAL SCIENCE

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Introduction

Young- and late-onset RA (YORA and LORA) have been described as two separate entities with a different prognosis [1]. YORA usually commences between 30 and 40 years of age, while RA developing after 60–65 years of age is usually called LORA [2, 3]. The incidence of RA has been described as continuously increasing, reaching a peak at between 70 and 79 years of age [4]. Consequently, in the ageing populations in many countries around the world, LORA will most likely gain in importance during the coming decades. Despite this growing importance, LORA has rarely been investigated in detail. Previous reports have suggested that the onset of LORA is more sudden than in younger patients [3]. Disease progression appears to be similar among LORA and YORA patients [5, 6]. LORA is as damaging [2, 5] or even more damaging [7] than RA of younger onset. The literature is divided with respect to joint deformities, which have been described either as less [8] or more [7] frequent in LORA. In contrast, the functional classification determined by the method of Steinbrocker *et al.* [9] did not change significantly despite treatment, and complete remission has been called unusual. The use of DMARDs and low doses of prednisone are the preferred therapies in LORA patients [6]. It has been suggested that the use of DMARDs is less frequent than in younger patients [7].

Predicting future disease progression is particularly important in early RA, as it may lead to personalized medicine tailored to the individual patient. LORA, in general, does not present a better prognosis than young-onset disease [7]. Acute phase reactants, RF and ACPA [10, 11] are important prognostic factors for all RA patients. Furthermore, HLA-DR4 and high levels of acute phase reactants at onset have been shown to be associated with poor radiographic outcome in LORA patients [2, 8]. Even though its prevalence increases with age, it is unclear whether RF is more frequent in LORA patients than in patients with earlier disease onset: higher [8] and lower [12] percentages of RF have been described for LORA patients. Ranganath *et al.* [13] found that acute phase reactants were higher in LORA patients. However, differences in CRP and ESR in elderly and younger RA patients vanished when these factors were corrected for patient age.

The aim of this study was to analyse disease activity, serological factors at disease onset and clinical and radiographic disease progression of LORA patients with the Swiss Clinical Quality Management in RA (SCQM-RA) cohort. We compared early RA patients of late and young disease onset.

Methods

Study population and design

The SCQM-RA is a population- and hospital-based RA cohort that has been described in detail elsewhere [14, 15]. The SCQM has obtained Swiss-wide ethics approval to collect patient data and broad consent to perform clinical research related to its aims. Since this project falls into the outlined research aims, no particular ethical approval was needed to perform this analysis on anonymized patient data. In this study we restricted our analysis to patients with early RA or undifferentiated arthritis (UA). The analysis includes data collected between January 1998 and November 2011. Inclusion criteria for the analysis were a diagnosis of RA or UA by a rheumatologist, and early disease, defined as $<$367 days of disease duration after the first symptoms (as defined by the patient). Patients treated with corticosteroids, synthetic DMARDs or biologic DMARDs for $>$31 days before the first visit were excluded from the analysis. Other exclusion criteria were missing 28-joint count at baseline or the absence of follow-up visits.

Outcome parameters

The primary endpoint was the change of DAS28 scores in the different patient groups. The DAS28 scores were calculated employing the swollen and tender joint counts, ESR and/or CRP. If both ESR-DAS and CRP-DAS were available, the average of both scores was used as previously described [16].

Secondary endpoints were radiographic changes and functional disability. Functional disability was assessed with the HAQ. The radiographic outcome was analysed on serial radiographs according to the number and size of bone erosions. Erosions were measured prospectively using a validated scoring system (Ratingen score), based on the amount of joint-surface destruction for each joint. The interobserver agreement and test–retest reliability are high, as published [17]. The pre-diagnostic radiological progression was calculated by baseline Ratingen score divided by disease duration (difference between the first symptoms and symptom duration at the baseline visit).

Statistical analysis

The baseline disease characteristics of patients in the two groups were compared using standard descriptive statistics. Continuous variables were compared using a Student's *t*-test, and categorical variables with the χ^2 test. Curves showing changes in DAS28 and HAQ scores over time were created using loess smoothing of the raw data. The effect of LORA/YORA on DAS28 and HAQ scores was estimated using linear mixed models with random slope and random intercept and adjusted for various baseline factors in a univariate fashion. Slopes of the Ratingen score before and after diagnosis were compared between groups using the Mann–Whitney *U*-test. All statistical analyses were two-sided at the 0.05 significance level. The analyses were performed using Excel (version 14.2.2; Microsoft, Redmond, WA, USA), the GraphPad Prism 5 software (GraphPad Software, La Jolla, CA, USA) and the lme4 package in *R* (R Project, Vienna, Austria).

Results

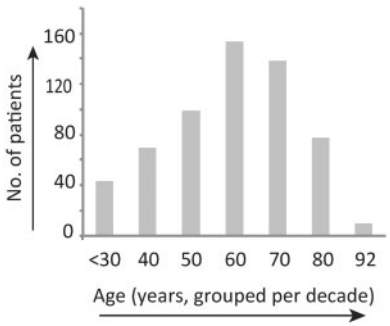
Patients

Of the 9627 patients in the database, 1345 had a disease duration <367 days at baseline, 947 patients were not pre-treated with any corticosteroid or DMARD for >31 days at baseline; 756 patients could be classified as having RA or UA, 609 patients had at least one follow-up in the database and 592 patients in the database had valid 28-joint counts. The median follow-up for these 592 patients was 44 months (range 0–178), representing 3845 visits.

Age at disease onset

To delineate whether two distinct patient groups may exist, the numbers of patients were analysed at the time point of disease onset depending on the patients' age. This grouped analysis resembled a Gauss distribution with a single peak between 50 and 60 years (Fig. 1).

Fig. 1 Correlation of age and disease onset



Patients were grouped per decade depending on their age at disease onset. The upper age level of the analysed patient group is depicted on the *x*-axis. Data are presented as the number of patients per group.

Baseline demographic data

Patients were categorized into two groups: YORA ($n = 366$, <60 years of age) and LORA ($n = 226$, >60 years of age). Analysis of the demographic data demonstrated that YORA patients were more likely to be female: 76.8% of the YORA patients were female, compared with 70.3% of the LORA patients ($P = 0.0131$). Follow-up (44.2 *vs* 55.4 months, $P = 0.0002$) and disease duration (167.2 *vs* 183.4 days, $P = 0.0002$) were both somewhat shorter among LORA patients. Clinically, no differences were found for the number of tender and swollen joints in the two groups. LORA patients displayed higher DAS28 and Ratingen scores, CRP levels and ESR at disease onset compared with YORA patients (Table 1). These differences were no longer visible after correction of ESR for age.

Treatment strategy

First-line treatment was variable. Comparing the first-line treatments, corticosteroids were used in 68% of the LORA patients as compared with 25.4% of the YORA patients (χ^2 test: 54.58, $P < 0.0001$; Fig. 2B). In contrast, first-line DMARDs were used in 100% of the younger patients compared with 91.2% of the older patient group.

During follow-up, up to nine treatment adjustments were made per patient. An average of 3.25 treatment adjustments (0.70 decisions/year) were made among YORA patients, compared with 2.73 among LORA patients (0.74 decisions/year; Fig. 2A). With regard to the number of adjustments for changing therapy to a new synthetic or biologic DMARD, this decision was made in 61.1 and 14.1% (synthetic and biologic DMARD, respectively) of all decisions documented among YORA patients and 54.6 and 6.6% in LORA patients (χ^2 test: 7.08 and 22.53, respectively; both $P < 0.01$).

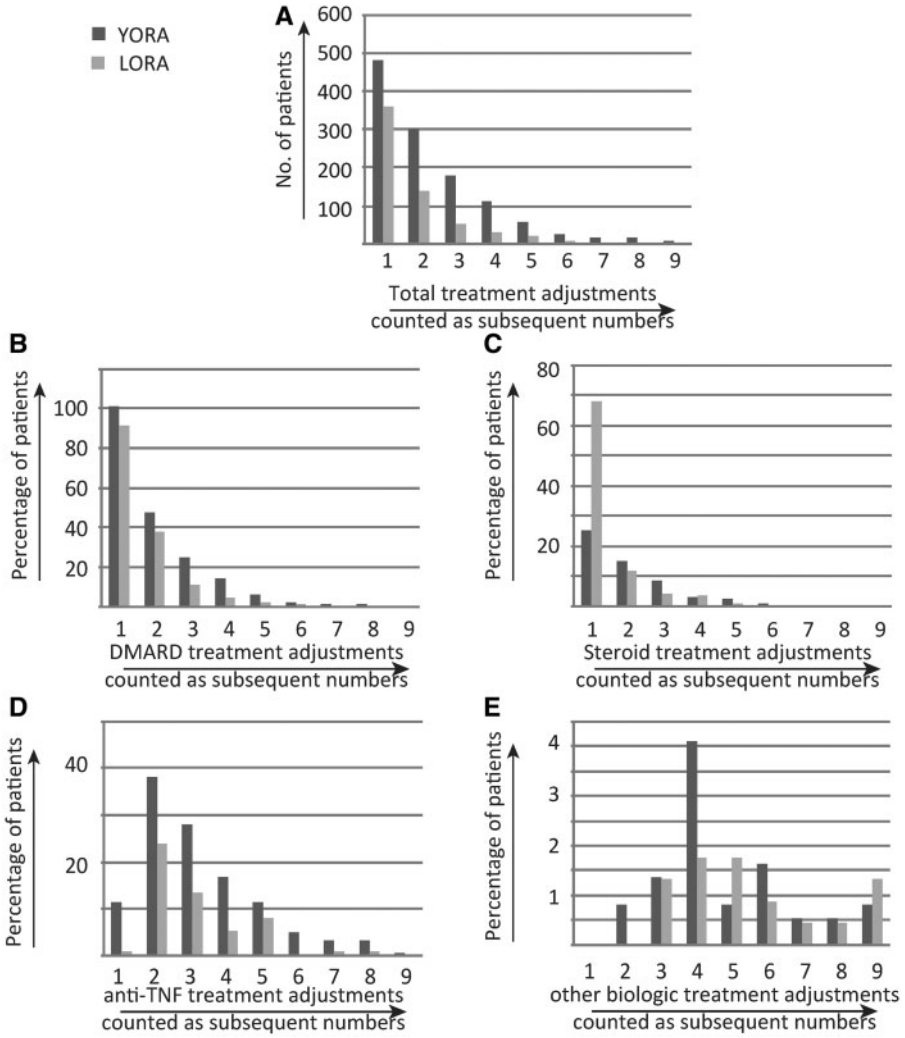
Glucocorticoids were initiated in 32.8 and 17.5% of LORA and YORA patients, respectively, during follow-up (χ^2 test: 54.4, $P < 0.0001$).

Table 1 Patient characteristics

	YORA	LORA	*P*-value
Number	366	226	—
Age, mean (S.D.), years	44.4 (11.0)	68.5 (6.3)	<0.0001
Sex, female/male	281/86	159/77	0.013
Follow-up, mean (S.D.), months	55.4 (39.9)	44.2 (33.3)	0.0002
Disease duration, mean (S.D.), days	183.4 (98.4)	167.2 (94.7)	0.047
SJC at onset, mean (S.D.)	7.4 (6.0)	8.0 (5.9)	0.23
TJC at onset, mean (S.D.)	8.1 (7.1)	7.5 (6.0)	0.31
DAS28 at onset, mean (S.D.)	4.4 (1.6)	4.7 (1.5)	0.0489
RF positive at onset, *n* (%)[a]	258 (70.5)	130 (57.5)	0.013
CCP positive at onset, *n* (%)[a]	99 (67.8)	52 (55.9)	0.06
ESR at onset, mean (S.D.), mm/h	25.6 (23.5)	32.3 (23.7)	0.001
CRP at onset, mean (S.D.), mg/l	16.5 (9.6)	24.5 (14.6)	0.15
Ratingen score at onset, mean (S.D.)	5.6 (6.9)	12.7 (11.3)	<0.0001

TJC: tender joint count; SJC: swollen joint count. LORA: late onset RA: >60 years of age; YORA: young onset RA: <60 years of age. [a]Calculated on patients with available data.

Fig. 2 Treatment strategy



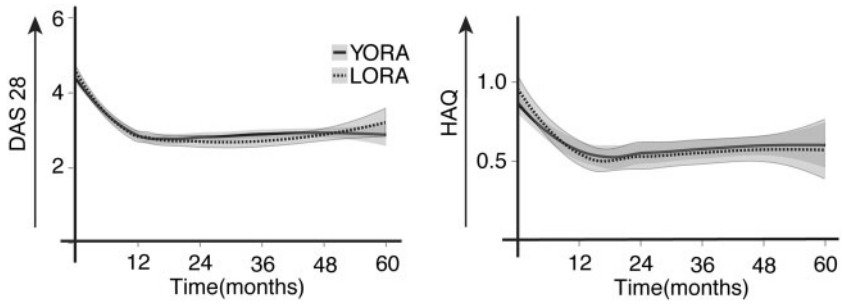
Individual treatment decisions were analysed for the two patient groups, younger patients in dark, older patients in light grey. The number of adjustments made at the different subsequent points in time (a maximum of nine decisions were analysed per patient) are shown per patient group independent of which therapeutic adjustment was made. Treatment changes are depicted as the total number of adjustments (**A**) or percentages of patients (**B**–**E**) for whom a decision was made. In detail, the total numbers or the percentage of total initial patients is shown who underwent a treatment change independent of a particular change (A), synthetic DMARD therapy (B), change of corticosteroid regimen (C), TNF antagonist treatment (D), and non-anti-TNF biologic treatment (E).

Clinical and radiographic progression

Disease activity at disease onset, assessed by DAS28 scores, was higher among LORA as compared with YORA patients. During follow-up, this difference vanished and no further difference was detected during follow-up comparing the statistical means of both groups (Fig. 3, left panel). In parallel, no difference for HAQ scores could be found during follow-up (Fig. 3, right panel). Adjusting for time to diagnosis, gender, age, medications and baseline RF, DAS28, Ratingen, HAQ, ESR or CCP scores, there were no statistically significant differences in changes in either DAS28 or HAQ scores over time between YORA and LORA patients (linear mixed models with random slope and intercept, each adjusting for one of the above mentioned factors, $P > 0.1$).

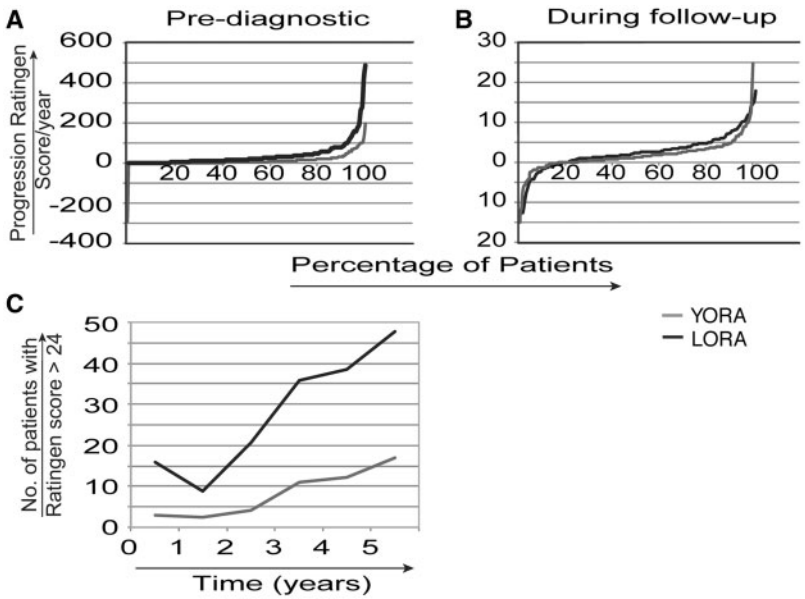
Radiographic progression was analysed using cumulative probability plots. The estimated pre-diagnostic radiographic progression was higher in LORA patients (Fig. 4A). However, during follow-up radiographic damage progressed at similar rates in both groups (Fig. 4B). When radiographic progression was analysed separately for low (Ratingen score 0–24) and high rates of destruction (Ratingen score > 24) in YORA and LORA patients, analysis revealed some differences. Of the initial 97.0% of

Fig. 3 DAS28 and HAQ scores over time



Patient groups were analysed separately for YORA (solid lines) and LORA patients (dotted lines). Loess smoothed time courses of DAS28 (left panel) and HAQ (right panel) are depicted per group over 60 months of follow-up with the 95% confidence interval as grey shade for each group.

Fig. 4 Radiographic progression



Radiographic progression was analysed employing the Ratingen scores over time: (**A**) pre-diagnostic and (**B**) yearly radiographic progression after diagnosis and initiation of therapy are shown as cumulative probability plots. LORA patients are depicted in black and younger patients in grey. The pre-diagnostic radiological progression was calculated using the Ratingen score divided by the time difference between the first symptoms and the first visit. For the progression during follow-up, the change in Ratingen scores was divided by the time between the different radiographs and yearly progression under therapy was calculated. (**C**) Percentage of patients developing a Ratingen score >24 over time.

YORA patients with low radiographic progression, 83.1% stayed in this radiographically low active group and the average percentage of patients with high radiographic progression increased from 15.4 to 47.4% of the LORA patients (χ^2 test for Ratingen scores >24 after 5 years: 63.33, $P = 0.0002$).

Concomitant diseases

The number of co-morbidities was analysed for the patients in our cohort (Table 2). At disease onset, no differences in either the number or kind of concomitant diseases were observed. However, during follow-up 0.54 concomitant diseases per year on average developed in LORA patients as compared with 0.32 in YORA patients ($P = 0.0001$).

Discussion

In this study we analysed a group of 592 RA patients with early disease depending on the age of onset. In our study, older patients showed a slightly higher disease activity

Table 2 Concomitant diseases

	YORA, *n* (%)	LORA, *n* (%)	*P*-value
Concomitant disease at baseline per patient	9.6	9.1	0.91
New concomitant disease developed during follow-up/patient-year	0.32	0.54	0.0001
Most frequent concomitant diseases at diagnosis and during follow-up			
Arterial hypertension	296 (80.9)	184 (81.4)	0.82
Diabetes mellitus II	293 (80.1)	171 (75.7)	0.21
Malignant tumour	294 (80.3)	170 (75.2)	0.14
Chronic cardiac disease	291 (79.5)	170 (75.2)	0.22
Alcohol/drug abuse	295 (80.6)	167 (73.9)	0.06
Chronic obstructive pulmonary disease	291 (79.5)	169 (74.8)	0.18
Cerebrovascular disease	292 (79.8)	168 (73.3)	0.12
Chronic nephropathy	292 (79.8)	168 (74.3)	0.12
Psychological diseases/depression	289 (79.0)	168 (74.3)	0.19
Gastric ulcer	291 (79.5)	165 (73.0)	0.07
Degenerative spondylopathy	287 (78.4)	167 (73.9)	0.03
OA	4 (1.1)	11 (4.9)	0.005

and more joint erosions at disease onset compared with younger patients. As the disease duration was shorter among LORA patients, this may reflect more aggressive disease rather than a longer, smouldering process before diagnosis.

The border between LORA and YORA has been defined differentially in the literature. Some authors define LORA after the age of 65 [2, 5, 7, 12, 18], while others use the age of 60 [1, 6, 19–21] or even as low as 55 years of age [13]. The average age of the patients in this study was 53.6 years (S.D. 15.1, median 55). Since the patients were grouped per decade for the analysis, we chose as the border between LORA and YORA the age of 60 years. Parallel calculations were also performed for a cut-off at 55 and 65 years. The results did not differ significantly using these different age thresholds.

These data raise three major questions:

Is LORA a separate form of RA?

Ferraccioli *et al.* [5] established the concept of a disease separated into two entities depending on the prognosis and age of the patients. They found no difference after the analysis of demographic, serological, and clinical data and scintiscan pictures. In our study, the significant clinical differences of the two groups at baseline were DAS28 scores, positivity for RF, ESR and Ratingen scores (Table 1). Looking at these factors in detail, the difference in ESR vanished if values were corrected for age, as previously published [22, 23]. When a ratio of the age and the corresponding ESR level was determined, this ratio was 0.47 for LORA and 0.57 for YORA. Thus, similar to data published by Ranganath *et al.* [13], the impact of higher ESR levels not only vanished, but was reversed, if ESR was corrected for the patients' age. If a value 6.7 mm/h for ESR (the difference of the average ESR levels found in the LORA and YORA groups at disease onset) is entered into the formula for calculating DAS28 values, the DAS28 value increases by 0.09 for DAS28 calculated using four variables and looses statistical significance [16].

The number of patients with substantial radiographic damage at baseline differed between the LORA and YORA patients in our study, increasing linearly with age (data not shown). Thus a clear separation of LORA from YORA, according to radiographic progression, as suggested by Fig. 4C, seems artificial.

Are older RA patients treated adequately?

Mavragani *et al.* [6] described that among Greek RA patients with LORA, DMARDs and low doses of prednisone represented mainstream therapy. This was similar in our cohort: LORA patients were more frequently treated with corticosteroids and less frequently treated with DMARDs or biologic DMARDs (Fig. 2).

This leads to two different assumptions: either LORA patients need more aggressive treatment, because they have more erosive disease at onset, as demonstrated by the higher Ratingen scores at baseline in our study, or, despite more erosions and a less aggressive treatment of LORA patients, the slope of evolving new erosions is similar to that of YORA patients. Since highly destructive disease as defined by a Ratingen score >24 was more frequent among LORA patients ($n=47$) at the end of our observation period than among younger patients ($n=17$) (Fig. 4C), an equally aggressive treatment for LORA patients seems advisable.

Are physicians more reluctant to initiate aggressive therapy in LORA patients because of co-morbidities?

The number of co-morbidities was analysed for the patients in our cohort (Table 2). Surprisingly, no differences in either the numbers or kinds of concomitant diseases were found at disease onset. However, the fact that 1.7 times more concomitant disease developed in LORA patients per year suggests that the presence of

co-morbidities may well have interfered negatively with the decisions for new therapeutics in LORA patients.

Conclusion

In summary, in our cohort, first, we found no clinical, serological or radiographic differences justifying a division of RA into two entities depending on the patient's age at disease onset. Secondly, and potentially more importantly, our results suggest that LORA patients, if their co-morbidities allow it, should be treated as aggressively as younger RA patients.

Rheumatology key messages

- Division of RA into two entities depending on the patient's age cannot be justified.
- Late-onset RA patients should be treated as aggressively as younger RA patients, depending on their co-morbidities.

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